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17 have been added herein. Thus, claims 1 to 3 and 6 to 17 are presently under examination.

Regarding the Amendments and New Claims

Attached as Exhibit A is a marked up copy of the amendments to the specification and claims showing language to be added by underlining and language to be deleted in brackets.

The specification has been amended to more clearly indicate that "peptoids and peptidomimetics" are not considered to be "peptides." The amendment is supported by knowledge well known to those in the art, who would recognize that a peptoid or a peptidomimetic can be distinct from a peptide, which is a molecule containing a peptide bond.

The specification further has been amended to more clearly indicate that methods of construction of libraries of "peptides, peptoids or peptidomimetics" are well known in the art. Support for the latter amendment is provided, for example, by the language deleted in the amendment to the specification discussed above. Thus, the amendments to the specification are supported by the specification or by knowledge in the art and do not add new matter. Accordingly, Applicants respectfully request the Examiner enter the amendments to the specification.

Claims 1 and 6 also have been amended to more clearly indicate that the claimed method relates to molecules that home to a selected "organ or tissue." The amendment is supported

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throughout the specification, for example, at page 18, lines 17-26, and, therefore, does not add new matter.

Claim 1 also has been amended in the preamble and in step (c) to more clearly indicate that a molecule that homes to a selected organ or tissue is "recovered" by isolating the molecule. The amendment is supported throughout the specification, for example, at page 9, lines 23-27, which indicates that phage expressing organ homing peptides were recovered from organs, and at page 15, line 32, to page 16, line 2, which discloses isolation of phage displaying organ homing peptides.

Claim 1 further has been amended to indicate that the recited library of diverse molecules is not a nucleic acid library. The amendment is supported in the specification, for example, at page 6, lines 18-31, which indicates that a library is a collection of molecules and that a molecule is an organic chemical such as a drug, peptide or protein.

New claim 7 is directed to a method of obtaining a molecule that homes to a selected organ or tissue, where the organ or tissue is a tumor. New claim 7 is supported throughout the specification, for example, at page 18, lines 17-23, and at page 22, lines 10-21, which indicate that the selected organ can be a tumor. Thus, new claim 7 is supported by the specification as filed and does not add new matter.

New claim 8 is directed to a method of obtaining a molecule that homes to a selected organ or tissue from a library

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of diverse peptides and peptidomimetics, and new claim 9 is directed to a method of obtaining a molecule that homes to a selected organ or tissue from a library of diverse peptides. New claims 8 and 9 are supported throughout the specification, for example, at page 6, lines 24-28, which indicates that a molecule can be a peptide or a peptide-like molecule such as a peptidomimetic.

New claim 10, directed to a method of identifying a molecule that homes to a selected organ or tissue, is supported throughout the claims and specification as originally filed, for example, in original claim 1 and in the specification at page 8, lines 3-20, which discloses identification of organ homing molecules. New claims 11 to 14 are supported, for example, by original claims 2 to 4 and 6, respectively. New claims 15 to 17 are supported as described above for new claims 7 to 9.

As set forth above, each of the claim amendments and new claims is supported by the specification or claims as originally filed and does not add new matter. Applicants therefore respectfully request that the Examiner enter the amendments and new claims.

Regarding the Objections to the Specification

The Examiner objects to the specification, for failing to indicate the present status, abandoned or patented, of the parent applications listed in the first paragraph of the specification. This paragraph has been amended herein to update the status of the priority applications and to identify issued

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patents. Applicants therefore respectfully request that this ground for objecting to the specification be removed.

The Examiner further objects to the specification for allegedly defining the terms "peptide" and "organ" in a manner that is inconsistent with the art. In this regard, the Examiner asserts that the term "peptide" has an art recognized meaning that does not include "peptides" and "peptidomimetics" and that the term "organ" has an art recognized meaning that does not include tissue, cells, and tumors.

The term "peptide" in the specification has been amended to delete reference to peptoids and peptidomimetics as included within the meaning of the term "peptide." In view of the amendment to the specification, Applicants respectfully request that the Examiner withdrawn this ground for objection.

The Office Action asserts that the definition of "organ" to include tissue, cells and tumors is contradictory to the art-recognized meaning of this term, which does not include tissues, cells and tumors.

Applicants submit that the definition of the term "organ" is consistent with the art-recognized meaning of this term as a part of an animal or plant body serving a particular function. Furthermore, the claims have been amended to recite a molecule that selectively homes to a selected organ "or tissue." In view of the above remarks and amendments, the Examiner is respectfully requested to remove this ground for rejection.

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Regarding the Rejection of claims 1 to 6 under 35 U.S.C. § 112,
second paragraph

The rejection of claims 1 to 6 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the invention is respectfully traversed. Claim 1 is allegedly incomplete for having a final method step that recites "identifying" but does not clearly relate back to the preamble. In claim 5, it is allegedly unclear whether "wherein said molecule is a peptide" applies to the molecule of step (c) or all the "diverse molecules" of the library.

While Applicants maintain that claim 1 is clear and definite as written, the preamble and step (c) of claim 1 have been amended to more clearly indicate that a molecule that homes to the selected organ or tissue is "recovered" from the sample of the selected organ or tissue. As such, step (c) clearly relates back to the preamble. Furthermore, while Applicants maintain that claim 5 also is clear and definite, this claim has been canceled herein in order to further prosecution of the subject application. In view of the above remarks and amendments, Applicants respectfully request that the Examiner remove the rejection of claims 1 to 6 under the second paragraph of 35 U.S.C. § 112.

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Regarding the Rejection of claims 1 to 3 and 6 under 35 U.S.C.
§ 112, first paragraph

The rejection of claims 1 to 3 and 6 and corresponding objection to the specification under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement, respectfully are traversed. The Office Action acknowledges that the specification enables methods of using a library of diverse molecules conjugated to a tag to provide recovery means or to a polynucleotide tag that can be amplified by PCR to provide identification means, yet asserts that the specification does not provide enablement for the full scope of the claimed invention.

Claims 1 to 6 are drawn to methods of recovering a molecule that homes to a selected organ or tissue by administering to a subject a library of diverse molecules that is not a nucleic acid library; collecting a sample of the selected organ or tissue; and recovering from the sample a molecule that home to the selected organ or tissue by isolating the molecule. Additional claims are drawn to methods of identifying a molecule that homes to a selected organ or tissue by administering to a subject a library of diverse molecules that is not a nucleic acid library; collecting a sample of the selected organ or tissue; and identifying a molecule that homes to the selected organ or tissue.

The Examiner raises several specific grounds as the basis for the enablement rejection: (1) alleged difficulties associated with "identification" of the homing molecules, which the Examiner asserts is necessary; (2) alleged difficulties

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associated with selection of starting libraries that will yield homing molecules; (3) alleged difficulties associated with tagging of library members; and (4) alleged difficulties associated with the use of untagged libraries.

(1) Applicants have previously argued in parent application Serial No. 09/227,906, now issued as U.S. Patent No. 6,306,365, and the Examiner has acknowledged that identification of a homing molecule is not necessary to practice the methods of claims 1 to 6. Applicants respectfully disagree that the only utility for the claimed invention is as an intermediate in a process for identifying individual homing molecules that can be used to direct compounds to a selected organ or tissue. Rather, a recovered molecule that homes to a selected organ or tissue itself can be useful as a binding reagent that can be linked, for example, to a radiolabel for diagnostic purposes or to a therapeutic moiety, without identification of the structure of the molecule. Given that the Examiner has acknowledged in the parent application that identification of the homing molecules is not required, Applicants submit that this ground for rejection is rendered moot.

(2) The Office Action contends that the specification does not teach any and all possible libraries of organic compounds nor which libraries other than polynucleotides, polypeptides and peptidomimetics would be likely to yield homing molecules. However, in the parent application, Applicants have previously argued that one skilled in the art would have been able to select a suitable library for use in the methods of the

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invention including, for example, a library comprised of several different libraries mixed together or a focused library designed around a lead compound. In allowing claims not limited to a particular type of library in the parent application, the Examiner has acknowledged that preparation of a variety of libraries and selection of libraries suitable for *in vivo* panning would have been within the ability of one skilled in the art at the time the invention was made. Applicants therefore submit that this ground for rejection is rendered moot.

(3) The Office Action asserts that several tags such as biotin or phage are taught in the specification for recovery and that a single type of tag (oligonucleotide) is taught for identification of library members. The Office Action concludes that the full scope of the invention has not been enabled. Applicants have previously argued in the parent application and maintain that one skilled in the art would have been able to practice the full scope of the invention with a variety of different tags including, but not limited to, biotin, hapten tags, oligonucleotides, phage and microbeads. Applicants have further submitted corroborating evidence that such technologies were well known in the art at the time the invention was made. In allowing claims in the parent application reciting a "tag that facilitates recovery of said molecules," the Examiner has acknowledged that the *in vivo* panning methods are enabled with tagged libraries. Applicants therefore submit that this ground for rejecting the claims has been rendered moot.

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(4) The Office Action alleges that undue experimentation would have been required to practice the claimed methods with untagged libraries.

Applicants submit that one skilled in the art would have been able to practice the full scope of the invention using tagged or untagged libraries without undue experimentation. In particular, one skilled in the art would have been able to recover a molecule that homes to a selected organ or tissue, or to identify a molecule that homes to a selected organ or tissue, using guidance in the specification and techniques routine in the art at the time the invention was made. In this regard, the specification provides guidance to the skilled person, teaching that one or more characteristics common to the molecules present in the library, such as a defined range of molecular weights, or polar or nonpolar characteristics (page 8, lines 7-32), can be useful in isolating homing molecules from unrelated cellular material. A sample from a selected organ can be processed, for example, using high pressure liquid chromatography to provide a fraction enriched in molecules having a defined range of molecular weights or having defined polar or nonpolar characteristics. As taught in the specification, methods for the bulk removal of potentially interfering cellular materials such as DNA, RNA, proteins, lipids or carbohydrates were well known in the art, as were selective extraction techniques based on differential solubility. As further guidance, the specification teaches that highly sensitive detection methods such as mass spectrometry, alone or in combination with gas chromatography, can be used to identify the structure of a homing molecule (page 8, lines 11-15). In sum, using the guidance in the

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specification, one skilled in the art would have been able to use routine microseparation techniques which do not rely on "tagging" of library members to recover and identify molecules that selectively home to a selected organ or tissue.

In view of the above, Applicants submit that one skilled in the art would have been able to practice the methods of the invention without undue experimentation using a variety of tagged and untagged libraries including, for example, tagged and untagged polypeptide, peptide, peptidomimetic and small molecule libraries. As corroboration that suitable microseparation techniques were known in the art at the time the invention was made, Applicants provide pre-filing date publications in which organic molecules were recovered and identified from tissue samples. Reddy and Tserng, Biochemistry 29:943-949 (1990), attached as Exhibit B, report that two new metabolites of vitamin D₂ were identified in isolated perfused rat kidney using ultraviolet absorption spectrophotometry and mass spectrometry (page 943, abstract). Similarly, Wiebe et al., J. Clin. Oncol. 10:990-994 (1992), attached as Exhibit C, utilize high performance liquid chromatography and mass spectrophotometry to identify estrogenic metabolites of tamoxifen in human breast tumor samples (page 990, abstract). These publications confirm that, at the time the invention was made, one skilled in the art would have been able to recover and identify small molecules present in complex tissue samples using routine techniques. As further corroboration that one skilled in the art would have been able to practice the methods of the invention without undue experimentation, Applicants provide herewith a Rule 132 Declaration evidencing that untagged small molecules were

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recovered and identified from tissue samples by mass spectrometry following intravenous injection of a small molecule library into a mouse. This Declaration, like Exhibits B and C, evidence that undue experimentation would not have been required to recover and identify small molecules that home to a selected organ or tissue.

One skilled in the art understands that the challenges inherent in recovering and identifying small molecule metabolites from tissue samples are similar to those inherent in recovering and identifying homing molecules, for example, from a focused small molecule library which is based on a core structure. In both cases, the structure of the molecule to be recovered and identified is unknown but shares a partial structure or characteristics with a core structure or "scaffold." One skilled in the art further understands that identification of a molecule that homes to a selected organ or tissue can be performed, if desired, by comparison to one or more purified, known compounds. For example, Wiebe et al. compare HPLC peaks from patient specimens to stock solutions of metabolite E to identify a tamoxifen metabolite in patient breast tumor samples (page 991, column 2, third full paragraph). Similarly, in the Rule 132 Declaration submitted herewith, brain and liver homing molecules recovered from tissue samples were identified based on comparison to known mass spectrometric results. Thus, given the state of the art at the time the invention was made, one skilled in the art would have had a variety of means available to recover and identify homing molecules as claimed.

One skilled in the art also would have been able to practice the methods of the invention with untagged peptide or

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polypeptide libraries, for example, using preparative two-dimensional polyacrylamide gel electrophoresis and tandem mass spectrometry to isolate and sequence the peptides. As an example, Applicants attach as Exhibit D Clauser et al., Proc. Natl. Acad. Sci. USA 92:5072-5076 (1995). Clauser et al. perform mass spectrometric peptide sequencing to identify 11 proteins in lysates of human melanoma cells (page 5072, abstract). These results confirm that, by comparison of 2-D gels of organ extracts from animals with or without library injection, protein spots can be selected, and subsequently eluted and sequenced in order to identify the protein or peptide. In sum, the Rule 132 Declaration and Exhibits B, C and D submitted herewith confirm that only routine microseparation techniques would have been required to recover and identify an untagged member of a library such as a polypeptide, peptide, peptidomimetic or small molecule.

In view of what is taught in the specification and further substantiated by publications known in the art at the time the invention was made as well as the Declaration submitted herewith, Applicants submit that undue experimentation would not have been required to practice the full scope of the invention. Accordingly, Applicants respectfully request that the Examiner remove the rejection of claims 1 to 3 and 6 under 35 U.S.C. § 112, first paragraph.

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Regarding the Rejection of claims 1, 2 and 6 under 35 U.S.C. §
102(e)

The rejection of claims 1, 2 and 6 under 35 U.S.C. § 102(e) as allegedly anticipated by Stephens et al., U.S. Patent No. 5,688,935, respectfully is traversed.

The cited patent by Stephens et al. allegedly describes a method for screening a library of diverse, non-naturally occurring, tagged nucleic acid molecules by panning against intact tissue samples *in vitro* or against tissue and organs *in vivo* such as brain, kidney, tumor tissue and arterial walls. The Examiner asserts that the method of Stephens et al. allows identification and isolation of individual library members.

As discussed above, independent claim 1 has been amended to more clearly indicate that the recited library of diverse organic molecules is not a nucleic acid library. Thus, the methods of the invention are practiced with a library of diverse molecules such as a library of polypeptides, peptides, peptidomimetics or small molecules. As such, the claimed methods are not anticipated by Stephens et al., which, at best, describes the screening of nucleic acid libraries. Absent the teaching of methods for screening a sample of a selected organ or tissue following administration of a library of polypeptides, peptides, small molecules, or other non-nucleic acid organic chemicals, Applicants submit that the claimed methods are patentable over Stephens et al.

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In view of the above remarks, Applicants respectfully request that the Examiner remove the rejection of claims 1, 2 and 6 under 35 U.S.C. § 102(e) over Stephens et al.

Regarding the Double Patenting Rejections

The rejection of claim 4 under 35 U.S.C. § 101 as allegedly claiming the same invention as that of claim 1 of U.S. Patent 5,622,699 is respectfully traversed. In view of the cancellation of claim 4, this rejection is rendered moot.

The rejection of claims 1 to 3, 5 and 6 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 to 5 of U.S. Patent No. 5,622,699; the rejection of claims 1 to 6 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 to 21 of U.S. Patent No. 6,068,329; the rejection of claims 1 to 6 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 to 10 of U.S. Patent No. 6,296,832; and the rejection of claims 1 to 6 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 to 19 of U.S. Patent No. 6,306,365 each is respectfully traversed. However, Applicants respectfully defer responding to the obviousness-type double patenting rejections until there is an indication of allowable subject matter in the present application.

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CONCLUSION

In light of the foregoing amendments and remarks, Applicants respectfully request that the claims are now in condition for allowance. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions relating to this application.

Respectfully submitted,

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